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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/349,925	07/08/99	CHANG, T	[illegible]012

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EXAMINER	
KERR, I	

ART UNIT	PAPER NUMBER
1653	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/349,925	CHANGEUX ET AL.	
	Examiner	Art Unit	
	Janet Kerr	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

Response to Amendment

The amendment filed 3/28/01 has been entered in part. The amendment to the specification has not been entered as the amendment does not comply with 37 CFR 1.121. Under the new amendment practice, amendments to the specification must be made by the submission of clean new or replacement paragraph(s), or section(s), as well as a marked-up version indicating the changes made (see the attached "Changes to the Patent Rules").

Claims 43 and 44 have been amended.

Claims 48-58 have been added.

Claims 40-58 remain pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-58 are/remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record and the reasons below.

As set forth in the Office action of 9/28/00 (Paper No. 5), the claimed invention is not enabled as the specification lacks guidance with respect to how to make and use the claimed transgenic mice comprising a specific fragment of the promoter of the β2-subunit of neuronal nicotinic acetylcholine receptor operatively linked to a nucleotide sequence encoding a

heterologous polypeptide selected from a toxin, growth factor, or oncogenic, tumorigenic or immortalizing protein, which is expressed in neurons of the transgenic mice.

Applicant's arguments filed 3/28/01 have been fully considered but they are not persuasive. It is argued that it would not require "undue experimentation" to make the claimed transgenic mice" as the specification discloses a particular promoter sequence to be used in the transgene construct to direct neuron-specific expression of heterologous reporter genes, such as β-galactosidase and luciferase, and substituting the reporter gene with other heterologous sequences would not require undue experimentation. It is argued that Aguzzi *et al.* (Brain Pathology, 4:3-20, 1994) teach well-characterized transgene constructs containing other neuron-specific promoters operatively linked to toxins, growth factors, and oncogenic, tumorigenic, or immortalizing proteins which were used to make transgenic mice that serve as models of neurological disease. It is also argued that Camper *et al.* teach transgene ablation studies in which various toxin genes were linked to different promoters and used to make transgenic animals.

With regard to the correlation between a specific toxin, growth factor, or oncogenic, tumorigenic, or immortalizing protein and a specific disease state or a particular change of function in the targeted neuron, it is argued that this type of information was known within the art and need not be disclosed in the specification. Applicants argue that as an example, Camper *et al.* teach using cell-specific promoters to direct cell-specific expression of immortalizing oncogenes in transgenic mice. The mice are useful for developing immortalized cell lines that can be used to identify transcription factors or gene expression. Applicants argue that the claimed transgenic mice can be used for similar purposes as disclosed in the instant application. Applicants also argue that Aguzzi *et al.* describe the correlation between various heterologous proteins and specific disease states, and therefore, as of applicants filing date, correlations were known to exist between heterologous proteins and specific diseases.

With regard to the level of expression of the heterologous proteins, it is argued that nonlethal expression level is a matter of routine screening and does not amount to undue

experimentation and furthermore, transgenic mice with lethal expression levels do not survive and would be readily distinguishable from transgenic mice with nonlethal expression levels.

With regard to the unpredictability of generating transgenic mice with a particular phenotype, it is argued that the references of Aguzzi *et al.* and Camper *et al.* more closely reflect the state of the art as of the filing date of the instant application than the references cited by the examiner. It is further argued that the references teach that those skilled in the art were using transgenic mice to direct tissue-specific expression of genes encoding toxins, growth factors, and oncogenic, tumorigenic, or immortalizing proteins and that such transgenic mice could be used to develop disease models, to develop cell lines, or to gain a better understanding of tissue-specific gene expression. It is also indicated that Aguzzi *et al.* demonstrate neuron-specific expression of genes in transgenic mice using neuron-specific promoters.

It is argued that the claims of the Meade *et al.* patent (U.S. Patent No. 4,873,316) are directed to broadly claimed process of producing "exogenous" protein using transgenic mammals having a casein promoter linked to an "exogenous" sequence, and that the claims were not limited to the single embodiment disclosed in the working example. This argument is not persuasive as each application is examined on its own merits. Moreover, the claimed invention of Meade et al is directed to a process for the production and secretion into mammal's milk an exogenous recombinant protein for the purpose of isolating the protein from collected milk. The phenotype and the utility of the transgenic mammal is readily apparent in the disclosure and the claimed invention. However, with regard to the instant claims, the specification lacks sufficient guidance for determining which toxins, growth factors, and oncogenic, tumorigenic, or immortalizing proteins are to be used, and lacks correlations between expression of the toxins, growth factors, and oncogenic, tumorigenic, or immortalizing proteins and the development of a particular disease model. What is the phenotype of the mouse which expresses a toxin, or a growth factor, or oncogenic, tumorigenic, or immortalizing proteins which can be correlated with a disease model. Which growth factor should be selected and what is the expected phenotype? Clearly one of skill in the art would first need to select a heterologous polypeptide of interest, produce the transgenic

mouse, determine whether the polypeptide is expressed and whether the expression is at a level to obtain a particular phenotype, analyze the mouse for a phenotype which is associated with some level of expression of the polypeptide, and determine whether the phenotype could be used as a disease model for example.

Applicants rely on the reviews of Aguzzi *et al.* and Camper *et al.* to establish that it is known in the art to generate transgenic mice which express the claim-designated polypeptides. However, these reviews do not provide sufficient guidance for one of skill in the art to know whether broadly claimed transgene constructs will be expressed in the mice at a suitable level to obtain a phenotype, what the phenotype would be, and how the skilled artisan would use the generated transgenic mouse in a disease model system, or what the phenotype of cells isolated from the transgenic mouse would be *in vitro*. The skilled artisan would not know how to use the claimed invention without further characterizing the generated mice or cells. Moreover, it is not readily apparent from the references of Aguzzi *et al.* and Camper *et al.* whether any transgene construct, and more particularly, applicants' construct would function to, for example, ablate neurons, or result in a transgenic animal which would be suitable as a disease model. Given a lack of disclosure of a specific heterologous protein to use in the transgene construct, and a particular phenotype associated with expression of the protein in neurons in a transgenic mouse comprising the construct, it would require undue experimentation to make and use the transgenic mouse as claimed.

The rejection is maintained for the reasons of record and the reasons above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43 and 44 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43 is vague and indefinite as it is unclear if the DNA of the second mouse is not identical to the DNA of the first mouse is referring to endogenous DNA or the transgene.

Claim 44 is rendered vague and indefinite as it is unclear if the DNA sequence is referring to the transgene or to endogenous DNA.

Applicant's arguments filed 3/28/01 have been fully considered but they are not persuasive. With regard to claim 43, it is argued that the second mouse has some difference in nucleotide sequence compared to the DNA of the first mouse, therefore, the second mouse could belong to a different strain than the first mouse or the second mouse could be a transgenic sibling of the first mouse. This argument is not persuasive as it is not clear from the claim what the genotype of the second mouse is relative to the first mouse. With regard to claim 44, it is argued that there is nothing vague or indefinite about a second mouse containing a DNA sequence different from the DNA sequence of the first mouse. This argument is not persuasive as it is unclear which DNA sequence is different, i.e., is the second mouse a different strain than the first mouse or is the second mouse a sibling of the first mouse with a different transgene or with the transgene of the first mouse and a second transgene. The metes and bounds of the claims are unclear.

Double Patenting

The examiner acknowledges applicants' request to hold the provisional obviousness type double patenting rejection in abeyance until the 08/465,712 application issues as a patent.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary Examiner of Art Unit 1633, at (703) 305-4051. Any administrative or procedural questions should be directed to Kimberly Davis, Patent Analyst, at (703) 305-3015. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401.

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